GAU 1632

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Applicant:	Clemons et al	**Group Art Unit: 1632**	
Serial No.:	09/435,257		
Filed :	November 5, 1999	**Examiner: Peter Paras, Jr.**	
For :	FK506-Based Regulation of Biological Events		

July 16, 2002

Assistant Commissioner of Patents
Washington, DC 20231

Petition for Extension of Time & Response to Office Action

Sir:

This paper is in response to the January 16, 2002 Office Action, a response to which was originally due on April 16, 2002. Applicants request a three month extension for responding and authorize the Commissioner to charge the fee due for such extension to Deposit Account No. 01-2315. The new deadline is now July 16, 2002. Accordingly, this response should be considered timely filed.

Restriction Requirement

We were disappointed by the rationale provided for maintaining the restriction requirement. Clearly a thorough prior art search of methods involving administering a ligand to a cell expressing applicants' novel fusion proteins—or any other use of the novel fusion proteins or materials containing the novel fusion proteins—is going to have to involve a search of the novel fusion proteins. For that reason we do not understand how, in practice, searching the different groups would involve an undue burden.

Imposing a restriction requirement is an exercise of the PTO's discretionary authority—it is not mandatory. In this case, restriction seems inconsistent with the PTO's principle of streamlined prosecution and will cause a hardship to the university assignee. For that reason, we ask respectfully that the finality of the restriction be lifted and that the restriction requirement be reconsidered and withdrawn.

Claim Objections and Rejections

The accompanying amended claims are believed to be free of any improper multiple dependencies or clerical errors and are believed to comport with 35 USC §101 and §112, 2d¶. In particular, GenBank reference numbers have been added to orient sequence numbering, claim 28 has been amended as suggested by the examiner and both claims 28 and 29 have been amended to correct a clerical error. A clean version of the amended claims is provided as Attachment A followed by a marked version as Attachment B. These amendments do not introduce any new matter. While no claim scope was intended or believed to be lost by virtue of the amendments, Applicants reserve the right to introduce and prosecute claims in this or related cases to any subject matter that may have been so lost.

Claim Rejections -- 35 USC § 112, 1st paragraph

Claims 26, 28, 30, 32, 34 and 38 stand rejected under 35 USC § 112, 1st paragraph on two grounds. As elaborated upon in the Office Action, applicants' disclosure allegedly fails to adequately disclose (1) how to create transgenic non-human animals expressing a CAB fusion protein to achieve a particular phenotype or (2) how to transduce a somatic cell in vivo with a nucleic acid encoding a CAB fusion protein, how to target a particular cell type, what the correlation is between expression of a CAB fusion protein and any particular resulting effect, what purpose other than therapeutic purposes there may be for expressing such genes in somatic cells. The Office Action also bases the enablement rejection on the alleged unpredictability of gene therapy.

We appreciate the Examiner's careful review of our dislosure and its ramifications, but we disagree in some respects with the legal analysis applied and disagree with his conclusions.

Let's look at the specification: the disclosure fills nearly 100 pages of text, describing the following, among other aspects:

- the operative design principles for designing and using CAB fusion proteins (see Summary of the invention and discussion on pages 16 – 21),
- specific details on nucleic acid sequences to start with (see e.g. the chart on p. 26),
- heterologous domains which may be included in the fusion protein design (see e.g. pp. 28 – 29)
- mutations that may be incorporated (see e.g. FKBP discussion on pages 21 – 24, cyclophilin discussion on p. 24, CAB discussion on pages 24 – 28)
- various ligands which may be used with the CAB fusion proteins (see e.g. pp. 33 – 34),
- additional components and design features which may be included (see e.g. pp. 34 35),
- tissue-specific or cell-type specific expression (see e.g. pp. 35 – 38, including chart of illustrative genes whose promoters/enhancers permit tissue-specific expression, with references, in many cases to transgenic animal experiments)
- target genes for heterologous expression (see e.g. pp 39 – 42)
- principles and practical guidance on design and assembly of DNA constructs (see e.g. pp 42 – 44)
- principles and practical guidance on the delivery of nucleic acids to cells ex vivo and in vivo (see disclosure beginning on p. 44 and continuing through viral vector systems on pp. 45 – 58, administration of viral vectors to recipients (p. 58 – 62)
- ligand binding properties and their measurement and comparison (see e.g. pp. 62 – 65)
- illustrative applications of the invention (see e.g. pp 65 - 68—including gene therapy, production of recombinant proteins and viruses, production of protein or RNA for biochemical purification, regulated expression of protein or RNA of interest for evaluation of function, etc.)
- practical guidance on formulation and administration of various materialsof the invention (see e.g. pp 68 – 72)
- 25 pages of specific examples
- 10 sheets of figures
- copious citations throughout the document to helpful references in the scientific and patent literature

Several important points need to be stressed

(1) The examiner has acknowledged that the specification has provided guidance for transformation of a cell in vitro with the claimed nucleotide sequences (pp. 3 and 7 Office Action). Applicants appreciate that acknowledgement and the implication of the adequacy of disclosure with respect to all of the prerequisite steps of nucleic acid design, assembly and delivery.

(2) Applicants have not belabored what was already in the art. That is as it should be: applicants have focused primarily on their contribution and have refrained from creating a treatise on techniques already in the

possession of the practitioner. For instance, a variety of methods and materials for creating transgenic animals and delivering genes in vivo were already in the art as of applicants' effective filing date (more on that below). Application of known techniques to applicants' CAB invention would fall well within routine work in this art—not undue experimentation.

(3) Applicants need not have optimized their invention for every conceivable application as a prerequisite for obtaining patent protection. Nor need they have optimized an embodiment to the point of establishing clinical efficacy. Proof of that sort of efficacy is required for FDA approval, not for satisfying 35 USC §112.

Transgenic animals

As of applicants' effective filing date, generating transgenic animals was a reasonably predictable art and a useful tool deployed both by industry and academia, achieving sufficient levels of transgene expression to make their use commercial and patentable.

The ability of the prior art practitioner to generate stable, functionally expressing, transgenic animals is reflected in the number of patents issued by the USPTO in the years prior to our application's earliest priority date of Nivember 6, 1998 (based on USSN 60/107,473). In the table below are illustrative examples of patents on transgenics issued to the United States Government, Harvard College (assignee for this application), various pharmaceutical companies, hospitals and other universities. The existence of all of these patents tells us that the technology was available to the practitioner beginning well before applicants' effective filing date. The U.S. Government not only patented such technology but it also created a national database of targeted mouse mutations and transgenic mice, called TBASE, in the early 1990's (see URL: http://tbase.jax.org/docs/history.html).

Patent #	**Earliest Priority Date,** Filing date	**Issue Date**	**Title**	**Assignee**
US5087571	**19840622** 19880322	19920211	Method for providing a cell culture from a transgenic non-human mammal	**Harvard College**
US5434340	**19881205** 19920727	19950718	Transgenic mice depleted in mature T-cells and methods for making transgenic mice	**GenPharm International, Inc.**
US5174986	**19890705**	19921229	Method for determining oncogenic potential of a chemical compound	**GenPharm International, Inc.**
US5487992	**19890822** 19930628	19960130	Cells and non-human organisms containi predetermined genomic modifications an positive-negative selection methods and vectors for making same	**University of Utah (Mario Capecchi)**
US5387742	**19900615** 19910617	19950207	Transgenic mice displaying the amyloid-forming pathology of alzheimer's disease	**Scios Nova Inc.**
US5550316	**19910102** 19930129	19960827	Transgenic animal model system for human cutaneous melanoma	Fox Chase Cancer Center
US5489743	**19930119**	19960206	Transgenic animal models for thrombocytopenia	**Amgen Inc.**
US5530179	**19930303**	19960625	Transgenic immunodeficient animal models	Beth Israel Hospital
US5718883	**19930414** 19940217	19980217	Transgenic animal model for autoimmune diseases	**United States of America**

US5470737	**19930609** 19941003	19951128	**Stably-transformed cells expressing human thiopurine methyltransferase** (includes transgenics)	Mayo Foundation for Medical Education and Research
US5824837	**19930722** 19960422	19981020	Expression of human interleukin-1B in a transgenic animal	**Merck & Co., Inc.**
US5932780	**19940228** 19950109	19990803	Transgenic non-human animal assay system for anti-cholinesterase substances	Yissum Research Development Company
US5792901	**19940513** 19960730	19980811	Method of detecting prions in asample a transgenic animal used for same	University of California
US5698766	**19950405**	19950405	Transgenic animal model fortesting drug treating eating disorders and epilepsy	University of California
US6187991	**19950523**	20010213	Transgenic animal models for type II diabetes mellitus	**Pfizer Inc**
US6262337	**19970218** 19980218	20010717	Transgenic animal with recombinant vascular endothelial growth factor B (VEGF-B DNA) and uses thereof	Ludwig Institute for Cancer Research
US6133502	**19970310** 19980309	20001017	Monocyte chemoattractant protein and its receptor transgenic animal	**Takeda Chemical Industries, Ltd.**
US6201165	**19971016** 19981015	20010313	Transgenic animal models for cardiac hypertrophy and methods of use thereof	University of Texas
US6118044	**19971114** 19981113	20000912	Transgenic animal allergy models and methods for their use	**Sankyo Company, Ltd** / Tokyo Metropolitan Inst. of Medical Science

The scientific literature provides many examples of stable, useful gene expression from transgenes in numerous mammals including mice, goats, pigs, cows, and sheep. For instance, Harvard's US Patent 5,087,571 summarizes numerous examples in the following passage:

> "Wagner et al. (1981) P.N.A.S. U.S.A. 78, 5016; and Stewart et al. (1982) Science 217, 1046 describe transgenic mice containing human globin genes. Constantini et al. (1981) Nature 294, 92; and Lacy et al. (1983) Cell 34, 343 describe transgenic mice containing rabbit globin genes. McKnight et al. (1983) Cell 34, 335 describes transgenic mice containing the chicken transferrin gene. Brinster et al. (1983) Nature 306. 332 describes transgenic mice containing a functionally rearranged immunoglobulin gene. Palmiter et al. (1982) Nature 300, 611 describes transgenic mice containing the rat growth hormone gene fused to a heavy metal-inducible metalothionein promoter sequence. Palmiter et al. (1982) Cell 29, 701 describes transgenic mice containing a thymidine kinase gene fused to a metalothionein promoter sequence. Palmiter et al. (1983) Science 222, 809 describes transgenic mice containing the human growth hormone gene fused to a metalothionein promoter sequence."

Gene Therapy

Again, with respect to the Examiner's concerns about whether gene therapy "works", with due respect, that is the wrong question. Applicants for patents are not required to optimize all conceivable embodiments of their inventions and are not required to optimize to the point of "working" as judged by FDA standards. By applicants' effective filing date the practitioner had a variety of materials and methods available for delivering genes in vivo. The specification provides a significant disclosure of illustrative materials and methods and provides copious literature references. To further illustrate that point, we provide as an attachment a partial survey of the patent and scientific literature dealing with the delivery of genes in vivo using AAV systems as alluded to in applicants' specification.

Claim Rejections -- 35 USC § 112, 2nd paragraph

This ground for rejection is believed rendered moot by virtue of the claim amendments.

Claim Rejections -- 35 USC § 102

Claims 1 -2, 4, 11, 20 - 21, 26, 28, 34, and 36 are rejected under 35 USC § 102(b) as being unpatentable under Guerini et al. (PNAS, 1989, 86. 9183-87). The examiner states that Guerini obtained the sequence from a human cDNA library and that the fusion protein was uncovered in a PTO sequence search, that was attached to the instant office action. Applicant did not receive a copy of that PTO sequence search (but would appreciate one in due course).

Regardless, we can say that Guerini (PNAS) does not teach or disclose the claimed invention. The reference discloses the cloning of Calcineurin A. Guerini does not disclose a CAB domain that "forms a tripartite complex with an FKBP/CAB ligand and an FKBP domain" as required by Claim 1. The reference is not seen to disclose fusion proteins of any sort, certainly not fusion prorteins containing any portion of Calcineurin B or of any of the heterologous domains recited in certain of the pending claims. Since anticipation requires the prior disclosure of each and every claim limitation, Guerini does not anticipate any of applicants' claims.

Claims 1, 3 - 4, 11, 20 - 21, 26, 28, 34, and 36 are rejected under 35 USC § 102(b) as being unpatentable under Guerini et al. (DNA, 1989, 8(9): 675-682) as teaching the cloning of said sequence into a vector that was transformed into a host cell *ex vivo*. The foregoing remarks are also believed to apply to the Guerini (DNA) reference, which is also not seen as anticipating any of applicants' claims.

Claim Rejections -- 35 USC § 103

Claims 1, 5 - 11, 20, 23, 26, 28, 34, and 36 are rejected under 35 USC § 103(a) as being unpatentable under Guerini et al. (PNAS) or Guerini et al. (DNA) taken with Chaudhuri et al. and Crabtree (US 6,164,787) as prima facie obvious. The examiner states Guerini et al. (PNAS) and Guerini et al. (DNA) taught sequences containing portions of CnA and CnB and that "it was routine in the art and well within the purview of the ordinary artisan to create a nucleotide sequence that encode fusion proteins comprising a domain of a protein of interest and heterologous domain for the use in the two hybrid system to perform binding assays with other proteins".

The critical issue for the §103 analysis is whether any of the references themselves suggested making the necessary combination to reach the claims in question. If not, then the combination which seems so logical seems so only by virtue of a hindsight analysis. That is the case here.

None of the cited references suggest designing a fusion protein combining a portion of Calcineurin A and a portion of Calcineurin B, not for any purpose and certainly not to make a fusion protein which forms a tripartite

complex with an immunophilin or cyclophilin in the presence of a ligand. Absent such a suggestion all the record shows is the prior existence of components and their use for other purposes. While those components might have been used for applicants' purpose, they weren't—not until applicants came along.

Concluding Remarks

In view of the foregoing, applicants request reconsideration and allowance of their claims. If there are any remaining issues that might be resolvable by phone, applicants' attorney encourages the Examiner to call him at the number provided below.

Respectfully submitted,

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I hereby certify that this paper is being deposited with the United States Postal Service via First Class Mail under 37 CFR 1.10 on the date indicated above and is addressed to Commissioner of Patents, Washington, DC 20231

Signed Sue Wilson